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COLLEGE OF MEDICINE AND HEALTH SCIENCE

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MASTER OF PUBLIC HEALTH

Adverse effect of multi drug resistance tuberculosis treatment and associated factors at st peter TB specialized hospital and Gondar university hospital, Ethiopia

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Approved by the Examining Board

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Acronyms

BMI- Body Mass Index

CI: Confidence Interval

COPD- Chronic Obstructive Pulmonary Disease

DR-TB-Drug Resistant Tuberculosis

DST-Drug Susceptibility Test

DOTS-Directly Observed Therapy Short course

HIV/AIDS -Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome

LPA-Line Proven Assay

MDR-TB- Multi drug Resistant Tuberculosis

SPSS -Statistical Package for Social Sciences

TB- Tuberculosis

TICs- Treatment Initiating Centers

TSH-Thyroid Stimulating Hormone

UoG- University of Gondar

WHO-World Health Organization

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Abstract

Background: - Multi Drug Resistance Tuberculosis is a growing public health problem in all over the world. The treatment of Multi drug resistance tuberculosis is very important because of the risk of transmitting virtually untreatable drug resistant disease. When patients are not timely and appropriately assessed and managed for adverse effects of second line drugs the consequence will be life treating.

Objective: - To determine Magnitude of adverse effect in Multi drug resistance tuberculosis treatment and associated factors at St Peters TB specialized hospital and Gondar university hospital, Ethiopia.

Method: - Institution based retrospective cross sectional study was conducted from April 1-20, 2014. A total of 540 patients were enrolled in this study and data was collected using pre tested structured check list by trained health professional. The collected data was reviewed and checked for completeness before data entry, coded and entered to Epi-info version 3.5.1 and was exported to SPSS version 20 for descriptive. Bivariate and multivariate logistic regression model were used to identify the associated factors of adverse effects. The degree of association between independent and dependent variables was assessed by using odds ratio with its 95% confidence interval.

Results: -. A total of 486 (90%) patients had at least one adverse effect while on treatment of Multi drug resistance tuberculosis. The most common adverse effects are severe gastritis (72.96%) followed by Arthralgia (limit mobility) (40.74%) and psychiatric disorder (30.56%). Body mass index less than 16.5kg/m^2 [AOR: 2.83, 95% CI: (1.57-5.08)] and HIV positive patients [AOR: 2.34, 95% CI: (1.14-4.79)] are significantly associated with Multi drug resistance tuberculosis treatment adverse effect.

Conclusion: - The prevalence of common adverse effect on Multi drug resistance tuberculosis treatment was high. Nutritional and HIV status are the associated factors for drug adverse effect. Therefore, especial emphasis for malnourished and HIV co infected patients should be given while they are taking anti Multi drug resistance tuberculosis treatment at treatment initiating centers.

Key words: Multi drug resistance tuberculosis, adverse effect, second line drugs, magnitude

Introduction

1.1 Statement of problem

Multi drug resistance tuberculosis is a growing public health problem in all over the world. The treatment of MDR TB is very important because of the risk of transmitting when left untreated (1). One of the challenges facing patients treated with second-line drugs (SLD) is the toxic nature of these drugs (2).

WHO global TB report estimated that globally in 2012, data from drug resistance surveys and continuous surveillance among notified TB cases suggest that 3.6% of newly diagnosed TB cases and 20% of those previously treated for TB had MDR-TB. The highest levels of MDR-TB are found in Eastern Europe and central Asia, where in some countries more than 20% of new TB cases and more than 50% of those previously treated for TB have MDR-TB (3). About 60% of these cases occurred in Brazil, China, India, the Russian Federation and South Africa alone ("BRICS") countries (4).

Ethiopia is one of among 27 high MDR-TB burden countries that carry 87% of the total global burden and one of the four countries in Africa. A survey done 2011-2013 on drug resistance tuberculosis result showed that, 1.6% of new cases and 11.8% of retreatment cases in Ethiopia were resistance to isoniazid and rifampicin, (MDR-TB) (5).

MDR TB treatment is both toxic and expensive. The drugs have many side effects which cause to interrupt the therapy. Previous studies have shown that patients with drug resistant tuberculosis have lower response rates than those with drug susceptible isolates (6). Side-effects such as drug induced hepatitis, dyspepsia; exanthema and arthralgia were responsible for termination of therapy in up to 23% of patients during the intensive phase (7). Medication side-effects were also found to be significantly associated with defaulting (8).

Adverse effects of the drugs increase the bad outcomes of treatment like defaulters. A study carried out in Kyrgyzstan prisons, in 2007 reported that medication side-effects were among the most common reasons for patient non-attendance at DOTS clinics. The side-effects profile of TB chemotherapy is magnified in patients with concurrent HIV treatment and/or prior history of hepatitis (9), Those patients treated with second-line drugs for

multidrug-resistant TB, during which as many as 86% of patents may develop medication side-effects (10,11).

When patients are not timely and appropriately assessed and managed for adverse effect of second line drugs adverse effect is life treating. According to study on patients with HIV co infection in Mumbai hospital show that among 81 patients eleven patients were hospitalized for adverse effect during the study period. The main reasons for hospitalization were life-threatening events (severe renal impairment, hypokalemia), seizures or severe psychiatric symptoms. Hospitalization was generally short (less than a week) and only two of the eleven patients had to be hospitalized more than once; both of them for hypokalemia. Looking at final treatment outcomes, adverse effect might have contributed to defaulting of two patients and death of four patients (12).

Recognizing the magnitude of adverse effect of MDR-TB treatment helps to give emphasis for treatment initiating centers on evaluation and monitoring of adverse effect of patients while treating patients on MDR-TB and helps Ministry Of Health and program designers to fulfill laboratory set ups and to plan for ancillary medications for treating the adverse effects while establishing treatment initiating centers.

Identifying associated factors for the adverse effect of MDR-TB treatment helps treatment initiating centers and treatment follow up centers to give special attention for patients with the factors and helps to increase the treatment outcome of MDR-TB treatment.

However, there is no research done in Ethiopia previously that show magnitude and factors associated with adverse effect of MDR-TB treatment .Therefore, this study was designed to determine the magnitude of adverse effect of MDR-TB treatment and associated factors in Ethiopia.

1.3 Literature review

Timely and intensive monitoring and management of adverse effects caused by second-line drugs are essential components of MDR-TB control programmes. Treatment of MDR-TB is difficult because of second line drugs have high side effect rates in MDR-TB treatment that leads compromised success rates. Poor management of adverse effects increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity (4).

1.3.1 Magnitude of adverse effects of MDR-TB treatment

Adverse effect of MDR- TB treatment are high in magnitude and some of the adverse effect are severe and life treating. According to a study conducted at Nepal in 2009 with retrospective cohort adverse effect of second line drugs show that from a total 70 MDR- TB patients on second line drugs 74.3% experienced adverse effects of drugs ranging from mild to severe. From those patients around 9.9% of patients were having serious adverse effects requiring hospitalization which include severe adverse arthralgia, hypokalemia, suicidal ideation and hepatitis (13).

A study with retrospective review in 2013 at Peru from 60 patients showed that from mild to severe adverse effects in 10% patients (14).

According to a prospective study conducted at Mumbai in 2012 showed that overall, 71%, 63% and 40% of patients experienced one or more mild, moderate or severe AE respectively. AE were most commonly attributed to cycloserine, ethionamide and *p*-aminosalicylic acid. There were 151 episodes of AE during the study period, 29 of them severe. Life-threatening events were rare: only one patient experienced severe Hypokalemia eight weeks after treatment initiation and two patients (3.0%) experienced severe renal impairment, which was diagnosed after 16 and 24 weeks of therapy respectively (14).

A retrospective cohort study carried out at Egypt in 2009 show that the prevalence of adverse effect on MDR-TB patient's show that gastritis is the leading adverse effect that accounts 88.3% of patients, peripheral neuritis is the second leading adverse effect that accounts for 76.7%, hypothyroidism is the third common adverse effect with 44.4% of patients develops

hypothyroidism. Hypokalemia also account around 23.3 % of from those develop adverse effect and CNS complication is one adverse effect from treatment of MDR-TB in this study accounts 16.1% of cases. Gout arthritis contributes for 14.4% of adverse effect developed, 13.3% of patients develop ototoxicity and hepatitis also contributes for 8.3% of patients (15).

1.3.2 Associated factors of Adverse effect of MDR-TB treatment

Adverse effects of MDR-TB treatment were associated with one or more of the following factors.

1.3.2.1 Demographic Factors

Some demographic factors like being female is associated with increasing adverse effect of the drugs. According to retrospective cohort study conducted at Nepal show systematic manifestation of adverse effect like hypothyroidism was seen among female patients accounts 75% of total patients followed and hepatitis was observed only in female patients but, Arthralgia with hyperuricemia though more in male account 63.17 of patients (13).But a retrospective cohort study conducted in Peru showed that there was no significant difference between male and female (14).

Studies on adverse effect of MDR- TB treatment show that being older age increases the risk of adverse effect of the drugs. A prospective study conducted in 2013 at Nepal show adverse effect of MDR-TB treatment were more commonly observed among patients age above 40 years they accounts around 94.1 % from those patients developed adverse effect of the MDR-TB treatment (13). According to a retrospective study done in Peru among 144 MDR-TB patients show that, there is an increasing incidence of MDR-TB drugs adverse events as age increases (14). Overall, vulnerability to adverse reactions are more probable at older ages especially at a hepatotoxic level due to a significant reduction in clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution, as well as other factors affecting liver function (16),(17).

1.3.2.3 Co morbidity

Chronic illness increase risk of adverse effect of MDR-TB treatment. Diabetic patients with MDR-TB are at risk for poor outcomes. The presence of diabetes mellitus may potentiate the adverse effects of anti- tuberculosis drugs, like renal dysfunction and peripheral neuropathy.

Patients with MDR-TB may have renal insufficiency at the time of MDR-TB diagnosis or they may develop it later while on treatment secondary to use of injectable (4).

If patients have underling liver disease the risk of having adverse effect like hepatitis, will increase since liver is one the commonest organs which can be affected by anti TB drugs. Both first line and second line anti TB drugs can cause liver toxicity. On the other hand patients with MDR-TB who need second line anti TB drugs may have an underling liver disease. In both cases meticulous clinical and laboratory monitoring should be done to follow up the progress (4), (18). Co-infection with hepatitis B or C has proven to be a high risk for adverse drug effects (19), (20).

MDR-TB is often associated with higher mortality rates in the HIV-infected compared with the non-infected. However, the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of MDR-TB in the HIV-infected (21, 22). Adverse effects are more common in patients with HIV. The multiple medicines involved in MDR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. There are adverse effects common to both antituberculosis treatment and ART, which may result in added rates of adverse events (18).

1.3.2.4 Nutritional status

Studies show that nutritional status associated with increase the risk of adverse effect of MDR-TB treatment patients with body mass index more than 25 kg/m^2 (overweight and obesity) was also associated with adverse reactions. Limited information is available regarding this association, but a prior investigation reported that drug toxicity is high because obese patients receive high dose of drugs according to total body weight (23). Another study reported that obesity can have some effects on drug metabolism which could increase possibility of adverse events (24). But a retrospective study conducted in 2013 at Peru shows that from a total of 70 patients around 40, 57.14% of patients are with BMI ≤ 18.5 kg/m^2. Majority of patients 82.5% develop adverse effect of MDR-TB from those patients around 64.7% develop GI symptoms (14).

1.3.2.5 Behavioral factors

Smoking is reported to be associated with MDR- TB drug adverse reactions (25). A study done in Peru show that statistically significant association between smoking and liver toxicity due to Pyrazinamide, However, literature regarding this finding is limited and further studies are needed (14).

Alcohol use can predispose and accelerate hepatotoxic effects caused especially by isoniazid due to enzyme induction changes (26), (27). Cycloserine will have a higher incidence of adverse effect in patients dependent on alcohol or other substances, including a higher incidence of seizure (21).

The incidence of adverse effect of MDR-TB drugs increase with patients IV drugs users can also be associated with hepatotoxicity. Overall, drugs have several effects which might affect the liver's enzyme induction as well as predisposing to hepatitis infection especially among intravenous drug users (19), (20).

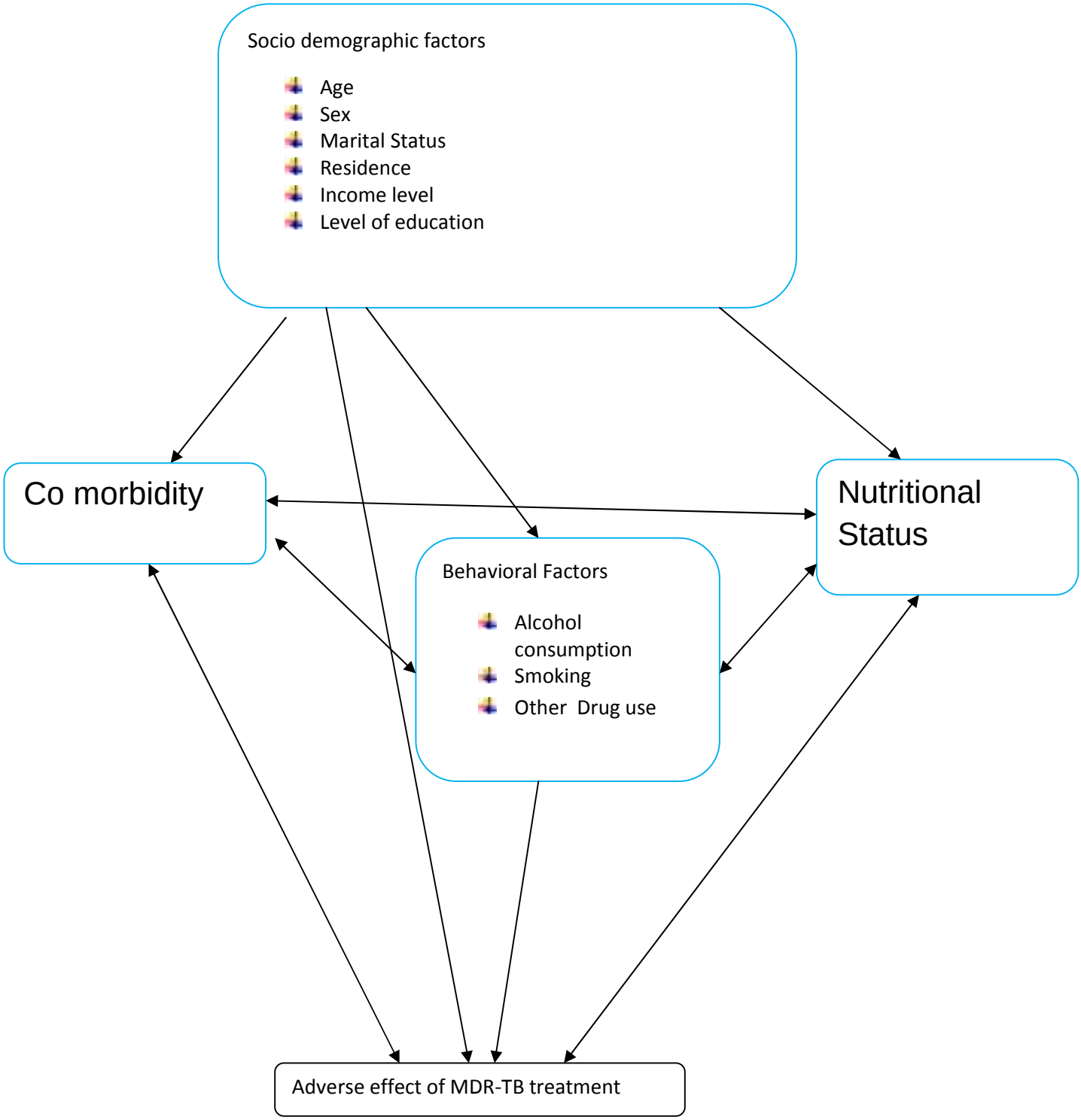
Socio demographic factors
Age
Sex
Marital Status
Residence
Income level
Level of education
Co morbidity
Nutritional Status
Behavioral Factors
Alcohol consumption
Smoking
Other Drug use
Adverse effect of MDR-TB treatment

Fig 1: Conceptual framework for factors affecting MDR-TB treatment adverse effect.

Justification

Now a day's the emergence MDR-TB is becoming a big challenge in the world because the way of transmission and the HIV/AIDS pandemic hasten the prevalence of the case. The challenge continue after the diagnosis because of the drugs of MDR-TB treatment was high cost and second-line drugs have many more adverse effects than the first-line Antituberculosis drugs (28).

The seriousness in severity and high in magnitude of side effect of second line drugs makes the treatment of MDR-TB more complicated and that need good laboratory setup and experts. So, more epidemiological data are necessary to assist policy makers and partners that going to escalate the treatment initiating centers of MDR-TB.

There is no study on magnitude of common adverse effect of MDR-TB treatment and associated factors this can cause the late detection of side effect that leads to poor out come and death. Absence of this adverse effect contributes to missed adverse effect that can affect the adherence of patient's negatively. Therefore this study will be aimed at measuring the magnitude of common adverse effect of MDR-TB Treatment and their associated factors, enables health professional to stress on adverse effect of the treatment to have a better outcome and policy makers and partners have big emphasis on MDR-TB treatment.

There is no evidence on associated factors of MDR- TB treatment adverse effect so, this study will be aimed to determine magnitude and factors associated with adverse drug reactions of MDR-TB treatment with special emphasis on MDR-TB medication, Co morbidity (HIV/ADIS, diabetes, chronic liver disease, chronic renal disease etc..), nutritional status, Behavioral factors (tobacco use, Alcohol use and other substance use) and socio demographic factors.

Therefore this study also used to evaluate the MDR-TB program and serve as a base line data for other researcher and for national MDR TB guide line.

2. Objectives

2.1 General Objective

To assess the prevalence of adverse effect on MDR-TB treatment and associated factors at St Peter TB Specialized Hospital and Gondar University Hospital, Ethiopia, 2014.

2.2 Specific objectives

- ✓ To measure the prevalence of adverse effect of MDR-TB treatment.
- ✓ To identify factors associated with adverse effects of MDR-TB treatment.

3. Methods

3.1 Study design and period

Institution based retrospective cross sectional study was conducted from April 1 to 20, 2014.

3.2 Study Area

There are around 20 TICs in Ethiopia but only three of them are organized and treating patients by second line drugs, the other sites now begin work by taking patients that start treatment from other TICs and some of them are on enrolling patients. These three senior TICs are St Peters TB specialized hospital in Addis abeba, Gondar university hospital and ALERT Hospital in Addis abeba. This study was conducted in two TICs St Peters TB Specialized hospital in Addis abeba and Gondar university hospital because the data are more organized.

St Peters TB specialized hospital is a general specialized Hospital under federal minster of Health. There are 676 patients totally enrolled in MDR-TB treatment since the begging of the St Peters Hospital is established as TIC.

Gondar University Hospital is the first referral hospital in North West Ethiopia expected to serve more than 5 million people. There are 183 patients enrolled in MDR-TB treatment since the establishment of GUH MDR-TB treatment initiating center.

3.3 Source and study population

The source population was all MDR-TB patients enrolled to MDR-TB treatment in the two treatment initiating center Hospitals. The study populations were patients enrolled in MDR-TB treatment and those took the drugs for more than 6 months.

3.3.1 Inclusion criteria

All patients those took MDR-TB treatment for more than 6 months.

3.3.2 Exclusion criteria

Those patients who have incomplete data files were excluded from the study.

3.3.3 Sample size Determination

Sample size was determined by using single population proportion formula by using the following assumptions:

In this study, sample size was determined using this formula

$$n = \frac{(z_{\alpha/2})^2 \; p\,(1-p)}{d^2}$$

Where

n = Sample size in

z_1 = 1.96 for 95% confidence level

P= 32.8 % Proportion of MDR-TB treatment drug adverse effect (18)

d= 0.05

n = 339

Since the numbers of patients who are taking MDR-TB treatment and fulfilling the inclusion criteria are 540, I have taken the entire patient to increase the power of the studies.

3.3.4 Sampling procedure

Since the number of patients on MDR-TB treatment were small this study was include all patients on MDR-TB treatment those fulfill the inclusion criteria.

3.4 Variables of the study

3.4.1 Dependent variable

MDR-TB treatment adverse effect (Presence/absence).

3.4.2 Independent variables

Socio demographic variables: Age, Sex, residence, marital status, Religion, educational status, occupation and Wealth index.

Behavioral variables: alcohol consumption, Smoking, kchat chewing and other substance abuse

Nutrition variable: BMI

Co morbidity: HIV/ADIS, Diabetes Mellitus, renal disorder, chronic liver disease, etc…..

3.5 operational definitions

MDR-TB: defined as TB caused by Organisms that are resistant to isoniazid and rifampicin, two first-line anti- TB drugs.

Adverse effect: - any unintended adverse response to a drug occurring at a therapeutic dose and resulting in either death, drug withdrawal, change in the administration of the frequency or dose of the drug or administration of other drug.

Hypokalemia: defined as when the serum potassium levels below 3.5meq/ml

Hypothyroidism: defined as when the serum thyroid hormone TSH level of > 4.25 mIU/L

Hyperuricemia: defined as when the serum uric acid level for female >5.6 mg/dl and for male >7 mg/dl.

Elevated creatinine: defined as when the serum creatinine for female >0.9 mg/dl and for male >1.2 mg/dl

Other chronic illness:-defined chronic illness other than HIV, Diabetes mellitus and chronic liver disease.

3.6 Data collection

The patients' files were assessed for the following data:

1. Socio demographic data of patients; Age, sex, occupation, residence, marital status, religion, ethnicity, educational status and Wealth index.

2. Co-morbidities; diabetes, COPD, hypertension, chronic liver disease, CRF and others.

3. Side effects of anti-tuberculosis drugs

1 clinical AEs: - gastritis, Neurologic side effect, ototoxicity, Arthralgia, rash, hepatitis.

2. Laboratory AEs: - hypothyroidism, Hypokalemia, Elevated liver function tests (SGOT, SGPT), Elevated creatinine level, Anemia

4. Nutritional status: BMI

5. Behavioral data: like alcohol consumption, smoking and any other substance abuse.

3.7 Data quality control

To assure the data quality high emphasis was given in designing data collection instrument. Before starting the data collection, the organized check list was pre-tested on 20 patients in st. Peter TB specialized hospital in Addis Ababa. Seven nurses and two health officers from that hospital was selected. Training was given for the data collectors and supervisors.

Throughout the course of the data collection frequent supervision was held on data collector and regular meetings was held between the data collectors and the principal Investigator together in which problematic issues arising on data collection.

The collected data was reviewed and checked for completeness before data entry;

The incomplete data was completed by contacting patients. Data entry format template was produced and programmed.

3.8 Data management and analysis

Data was checked, coded and entered to Epi-info version 3.5.1 and was exported to SPSS version 20 for analysis.

Data entry was made by the principal investigator. Binary logistic regression was fitted to identify factors associated with common adverse effect of MDR-TB treatment. In descriptive statistics tables, graphs mean and frequency was used to present the information. Significance was obtained at Odds ratio with 95% CI and $p< 0.05$.

4. Ethical consideration

Ethical clearance was obtained from Ethical review committee of university of Gondar. Communication with St Peter TB Specialized Hospital and Gondar university hospital was made in order to obtain permission letter.

Privacy and confidentiality of information taken from each chart was kept properly and names or personal identifiers were not recorded.

5. Dissemination of the result

The results of the study will be presented to University of Gondar, College of Medicine and Health Sciences, Institute of Public Health as part of master of public health thesis and it will also shared to Federal Ministry of Health, Amahara Regional Health Bureau, Gondar University Hospital and other treatment initiating center that launch the treatment. Efforts will be made to present the results on scientific conferences and peer reviewed journal publications will be considered.

6. Results

6.1 Socio- Demographic characteristics of the study participants

A total of 540 studies participants who had complete data were included. Among the total 59.8% were male and 40.2% female. The mean (SD) age of the patients were 30.89 (± 10.13) years. About 33.3% of patients have attended secondary schooling. Patients from urban were 71.3% and 46.5% of patients were married at the time of treatment. Majority of respondents were had no fixed income 62.2% and patients unemployed to any work at the time of treatment accounts 24.4%.

Table1. Socio-Demographic characteristics of MDR-TB patients at St Peters TB specialized hospital and Gondar university hospital, 2014.

Socio-Demographic and characteristics	frequency	Percent (%)
Sex (n=540)		
Male	323	59.8
Female	217	40.2
Age(year) (n=540)		
<20	37	6.85
20-24	125	23.15
25-35	228	42.22
36-45	96	17.78
>45	54	10
Educational status (n=540)		
No formal education	103	19.1
Primary (1-8)	120	22.2
Secondary (8-12)	180	33.3
More than secondary	137	25.4
Residence (n=540)		
Urban	385	71.3
rural	155	28.7
Marital status (n=540)		
Never married	211	39.1
Currently married	251	46.5
Separated	69	13.8
Widowed	9	1.7
Occupation (n=540)		
Government employee	69	12.8
Agricultural work	58	10.7

Merchant	38	7
Student	95	17.6
Housewife	100	18.5
Unemployed	132	24.4
Others	48	8.9
Monthly income(in Birr) (n=540)		
<500	336	62.2
500-1000	97	18
1001-2000	99	18.3
>2000	8	1.5

6.1.1. Behavioral and chronic illness history distribution of MDR-TB patients

As regarding co morbidity; 21.5% respondents were co infected with HIV and 10.6%of respondents were had history of cigarette smoking.

Table2. Behavioral and chronic illness history characteristics of MDR-TB patients at St Peters TB specialized hospital and Gondar university hospital, 2014.

Behavioral and chronic illness	Frequency	Percent (%)
Hx. Of smoking (n=540)		
Smoker	57	10.6
Non smoker	483	89.4
Hx. Of Alcohol (n=540)		
Yes	26	4.8
No	514	95.2
Hx. Chat chewing (n=540)		
Yes	16	2.96
No	524	97.06
HIV status (n=540)		
Positive	116	21.5
Negative	424	78.5
Hx. Of DM (n=540)		
Yes	10	1.85
No	530	98.15
Hx. Other chronic illness (n=540)		
Yes	17	3.15
No	523	96.85
Hx. Other medication in take (n=540)		
Yes	122	22.6
No	418	77.4

6.2 Prevalence of adverse effect

A total of 90% respondents were had at least one adverse effect while on treatment of MDR-TB. Among the adverse effects severe gastritis 72.96% toke the leading followed by Arthralgia (limit mobility) 40.74%.

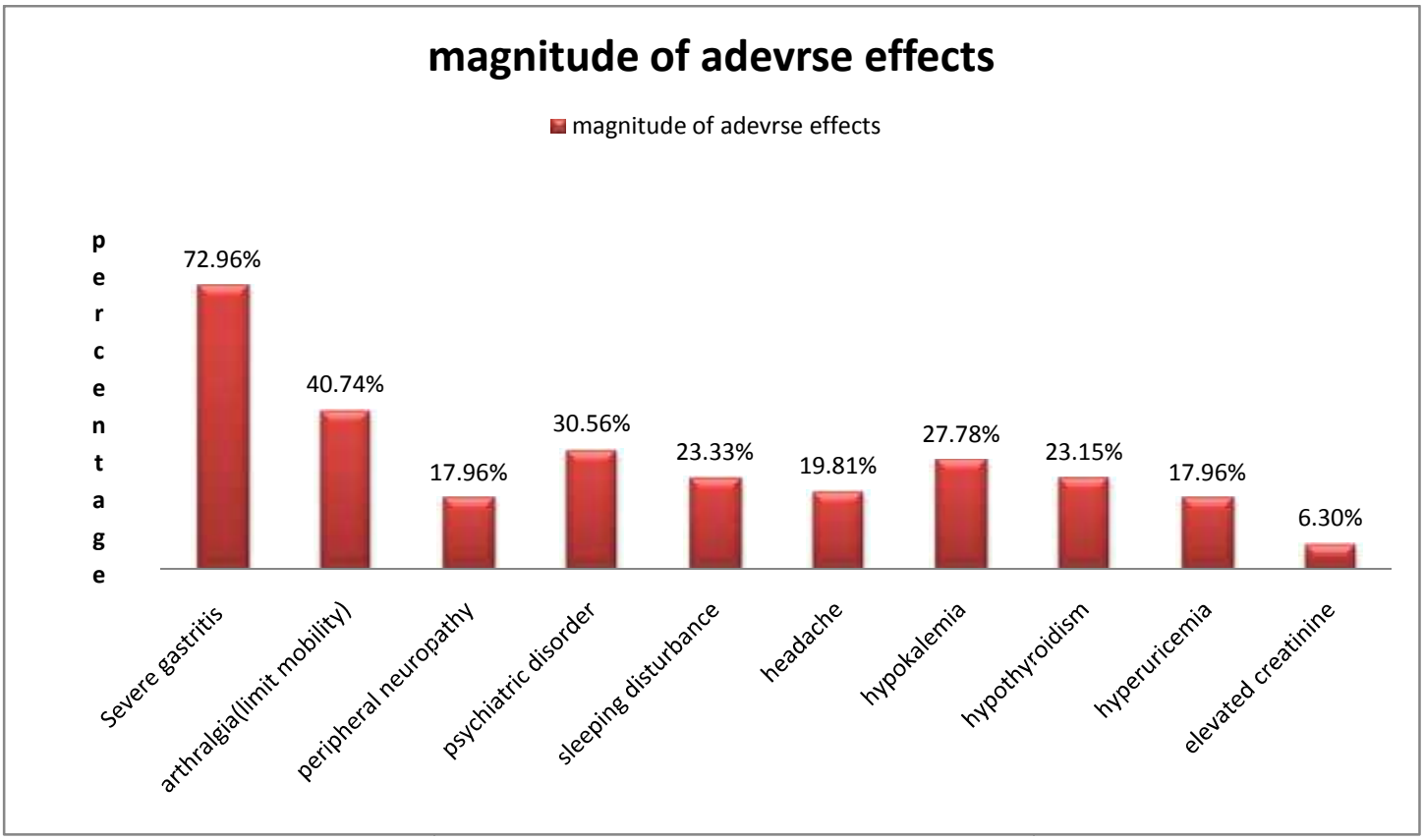

Figure2. Magnitude of each common adverse effect of MDR-TB patients at st Peters TB specialized hospital and Gondar university hospital, 2014.

6.2.1. Distribution of common adverse effect with socio demographic characteristics of patients.

Among total patients male patients were had magnitude of adverse effect 59.1% and age group 25-35 years were had magnitude of adverse effect 42.6%. According to this study from all patients unemployed patients were had magnitude of adverse effect 23.9% and patients with monthly income level <500 birr had magnitude of adverse effect 60.5%.

Table3. Socio-Demographic characteristics wise distribution of adverse effect of MDR-TB treatment at St Peters TB specialized hospital and Gondar university hospital, 2014.

Demographic and socio-economic characteristics	frequency	Percent (%)
Sex (n=486)		
Female	199	40.9
male	287	59.1
Age (years) (n=486)		
<20	27	5.5
20-24	107	22
25-35	207	42.6
36-45	92	18.9
>45	53	10.9
Educational status (n=486)		
No formal education	94	19.3
Primary education	106	21.8
Secondary education	164	33.7
More than secondary	122	25.1
Residence (n=486)		
Urban	347	71.4
Rural	139	28.6
Marital status (n=486)		
Never married	183	37.7
Currently married	231	47.5
Separated	63	13
Widowed	9	1.9
Occupation (n=486)		
Government employee	63	13.8
Agricultural work	54	11.1
Merchant	34	7
Student	70	16
House wife	94	19.3
Unemployed	116	23.9
Others	43	8.8
Monthly income level (n=486)		
<500	294	60.5
500-1000	90	18.5
1000-2000	94	19.3
>2000	8	1.6

6.2.3. Nutritional status of MDR-TB patients with distribution of adverse effect of MDR-TB treatment.

According this study patient with malnutrition BMI less 16.5kg/m^2 were had 44.4% of adverse effects while on treatment of MDR-TB.

Table4. Nutritional status of patients with distribution of adverse effect of MDR-TB treatment at St Peters TB specialized hospital and Gondar university hospital, 2014.

Nutritional status of patients on MDR-TB treatment	frequency	Percent (%)
BMI (n=486)		
<16.5	216	44.4
16.5-18.49	167	33.3
18.5-24.99	103	22.2

6.2.4. Distribution of MDR-TB treatment adverse effects with behavioral, history of chronic illness and history of any other medication in take than second line drugs.

Among total patients smokers 11.3% patients were developed any of the adverse effect while on treatment. Among total patients those with history of drinking alcohol 5.1% were reported they developed any of the adverse effects. From total patients HIV positive patients 22.8% were reported at least one adverse effect while on treatment of MDR-TB.

Table5. Behavioral, history of chronic illness and history other medication in take with distribution of adverse effect of MDR-TB treatment at St Peters TB specialized hospital and Gondar university hospital, 2014.

Behavioral, history chronic illness and other medication in take	Frequency	Percent (%)
Behavioral factors		
Of patients (n=486)		
Smoking history	55	11.3
Alcohol intake	25	5.1
Chat chewing	15	3.1
History of other chronic illness		
(n=486)		
HIV positive	111	22.8
DM	9	1.9
History of OCI	17	3.5
History of other medication in take		
(n=486)		
Patients take other medication	117	24.1

6.3 Associated factors of adverse effect of MDR-TB treatment

Socio-demographic, nutritional status, behavioral and co-morbidity with history other medication intake determinants in relation to presence of adverse effect were analyzed by bivariate and multi-variate analyses using logistic regression models.

This study shows that there is no statistically significant association between adverse effect and age group of patients. According to this study patients with BMI less than 16.5kg/m^2 were had 2.8 times more likely odds of developing adverse effect than other patients [AOR: 2.83, 95% CI: (1.57-5.08)].HIV positive patients had 2.3 times likely of developing adverse effect than other patients [AOR: 2.34, 95% CI: (1.14-4.79)]. Table6: Shows the association some variables with common adverse effects.

Table6. Bivariate and multivariate analysis showing the association of selected independent variables on common adverse effect of MDR-TB treatment at St Peters TB specialized hospital and Gondar university hospital, 2014.

Variables	Adverse effect		COR(95%CI)	AOR(95%CI)
	Yes (%)	No (%)		
Age (years)				
<20	27	10	1	
20-24	107	18	1.73(0.49-6.18)	
25-35	207	21	3.18(0.90-11.19)	
36-45	92	4	2.93(0.78-11.04)	
>45	53	1	2.88(0.69-11.843)	
BMI				
<16.5	216	16	2.75(1.38-4.14)	2.83(1.57-5.08)*
16.5-18.49	167	17	1.88(1.08-3.29)	1.97(1.10-3.51)
18.5-24.99	103	21	1	1
HIV status				
Positive	111	5	2.90(1.31-5.23)	2.34(1.14-4.79)**
Negative	375	49	1	1
Hx. Other medication in take				
Yes	117	5	3.10 (1.29-4.86)	
No	369	49	1	

Note: *p<0.05 ** P<0.01

7. Discussion

The proportion of common adverse effects was 90% [95% CI: 85-94.9].

Regarding associated factors of common adverse effects, multivariate analysis of this indicated that nutritional and HIV status were found to be significantly associated with common adverse effects.

According to this study the proportion of common adverse effects were 90% this result was in line with study conducted in Egypt which is 88% (15) but slight higher than study done in Nepal 74.3% and 52% in Peru (13, 14) and this result was lower than study done in south Africa which shows 98% (28) it might because of the socio-cultural characteristics of the population and nutritional levels of the patients.

Among common adverse effects gastritis were reported higher which accounts 72.96% this result was lower than study conducted in Egypt which was 88% it might be because due to our poor documentation of patient chart (15) but, this result was higher than study done in Nepal 21% and in Mumbai 45% it might because of difference in nutritional status of patients studied (14, 12).

According to this study the proportion of Arthralgia was 40.74% which is contrast with study conducted in Egypt 14.14% and Nepal 24.6% (15, 13) it might be due of the prevalence of HIV co infection was high in this study relative to Egypt and Nepal that increase the risk of Arthralgia, but this result was in consistence with study conducted in south Africa which was 40% (28).

Proportion of psychiatric disorder were 30.56% which was less than study conducted in south Africa 46%(28) it might be because of high proportion of patients was HIV co infection in south Africa but, this result was higher than study done in Egypt 16.1% it might be due to less HIV co infected patients in Egypt however, this result was in line with study conducted in Mumbai which 28%(15, 12).

This study shows that the proportion of Hypokalemia was 27.78% which higher than study conducted in Egypt 23.3%, but this result was less than study done in South Africa which shows 40% of patient's report Hypokalemia this difference might be due to the prevalence of HIV was high (15, 28).

In this study the prevalence of peripheral neuropathy were 17.96 % which in contrast with study conducted in Mumbai 37% and South Africa 74% respectively this difference might be because the above two study were conducted among HIV co infected patients (12, 28).

This study shows that there is no statistically significant association between adverse effect and age group of patients. However study done in Peru and Nepal show that age of the patients had significant association with presence of adverse effect (13, 14) whereas, age of the patients had not significant association with adverse effects study conducted in Egypt (15).

This finding revealed that, as the body mass index of patients decrease the risk of developing adverse effect increase. Patients with BMI < 16.5kg/m^2 were 2.83 times [AOR: 2.83, 95% CI: (1.57-5.08)] more likely to develop adverse effect. The finding of this was consistent with study conducted in Nepal and Peru (13, 14) respectively. This might due to poor nutritional status. Evident show that when patients had malnutrition especially PEM it associated with decrease the mucosal layer of the gastric that predispose patients to develop gastritis (24).

HIV infected patients had 2.3 times higher odds of developing adverse effect than HIV negative patients [AOR: 2.34, 95% CI:(1.14-4.79)] this result was in line with study done in south Africa and Mumbai(12, 28).

This finding might be due to HIV infected patients other medication than the anti TB drugs, among the medications ART was the main so patients on ART treatments some of this ART drugs like efanvirenz increase the risk of psychosis with the cycloserine and some drugs like stavudin increase the risk of developing peripheral neuropathy and HIV positive patients had more psychosocial problems and HIV by itself increase adverse effect like peripheral neuropathy (28).

8. Conclusion

The proportion of common adverse effect on MDR-TB treatment was high. Among the adverse effects the most common was severe gastritis followed by Arthralgia. Malnutrition and HIV co infection were significantly associated with the presence of MDR-TB treatment adverse effect.

9. Recommendation

Considering nutritional package for MDR-TB patients and fulfilling the laboratory setups while opening TICs to easily diagnose patients those develop adverse effect before they come up with unfavorable outcome was expected from Policy makers and program designer to get better outcome of MDR-TB treatment.

Especial emphasis for malnourished patients, HIV co infected patients and patients took other medication while on treatment of MDR-TB by TICs will improve the outcome of the MDR-TB treatment.

Patients on MDR-TB treatment should have to correct there nutritional habit to came up with better outcome of their treatment.

Researcher better if they study more on the specific adverse effect and its associated factors for each adverse effect with prospective cohort study design.

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10. Annex

Check list on magnitude of MDR-TB treatment adverse effect and its associated factors in selected TICs in Ethiopia, 2014

Identification

Code_____ (card number, serial number)

Part – I Socio- demographic information

Question		Response
1.	Sex	1. Male 2. female
2.	Age	Years----------
3.	Educational Status	1.No formal education 2.Primary 3.Secondary 4. More than secondary
4.	Residence	1.Urban 2.Rural
5.	Marital status at time of treatment	1.Never married 2.Currently married 3.separated 4.Divorced 5.Widowed
6.	Which of the following describes your main work status?	1.Health professional 2.Government Employee 3.Agricultural Work 4.Merchant 5.Spiritual Work 6.Soldier 7.Student 8.Housewife 9.Retired 10.Unemployed /unable to work/ 11.Unemployed /able to work/ 12.Other
7	Monthly wealth index in terms of money	---------- birr/month

Part II Anthropometric Measurement

8	Weight	In Kg----------
9	Height	In meter----------
10	BMI /body mass index	Kg/m^2

Part III Life style (Behavioral) information

Question		Response
11	Did the patient smoke cigarette?	1.Yes 2.No
12	If yes for how long have you the patient smoke?	----------(Y) months
13	On average how many cigarettes/day did the patient use?	----------
14	Did the patient drink alcohol products regularly?	1.Yes 2.No
15	If yes, What kind of Alcohol?	1.Tell 2. Beer 3.Areki 4.Other Specify ----------
16	On average how many bottles?	----------/day(week)
17	If yes, for question 15 how long have consumed alcohol?	----------(Y) months
18	Did the patient have history of Chat Chewing?	1.yes 2.No
19	Did the patient have history of other substance use?	1.yes 2.No

20	If yes, please specify	----------

Part IV Co morbidities information

Question		Response
21.	HIV status of the patient at time treatment?	1.posetive 2.Negative
22.	If positive, what is CD4 count at time of initiation of treatment?	1.<50 2.50-100 3.100-200 4.200-350 5..350
23.	Is the patient on ART treatment?	1.Yes 2.No
24.	If yes, how long have you been on ART	----------months/years
25.	Does the patient have history of Diabetes Mellitus?	1.Yes 2.No
26.	Does the patient have history of Chronic Liver Disease?	1.Yes 2.No
27.	Does the patient have any other chronic illness?	1.yes 2.no
28.	If yes, please specify	----------
29.	Does the patient taking other medications at the time of treatment on MDR-TB ?	1. Yes 2. No
30.	If yes please specify	----------

Part V History of treatment and Adverse effect Information

Question		Answer
31.	Doe the patient have any treatment adverse effect?	1.yes 2. no
32.	If yes, which clinical Adverse effect does the patient develop?	Clinical Adverse effect 1. Gastritis 2. Arthralgia 3. Ototoxicity 4. Peripheral neuropathy 5. Psychiatric manifestation (depression, anxiety, psychosis, suicidal ideation)

		6. Seizure 7. Rash 8. Headache 9. Sleeping disturbance 10. Other----------
33.	If there were any adverse effect at what month of treatment the patients develop the Adverse effect?	----------months
34.	What was the outcome of the patient with regard to the adverse effect?	1. Ancillary medication given 2. Drug dose decreased 3. The suspected Drug holding 4. Totally all drug holding 5. Suspected drug changed 6. Died 7. Defaulted
For laboratory detected adverse effects		
35.	Doe the patient have any treatment adverse effect?	1.yes 2.no

36. If yes, which laboratory Adverse effect the patients develop?	Answer	Lab. Test result	Month of Rx. The patient develop adverse effect
1. Elevated Liver function test (ALT) Normal range SGOT(0-31 u/l) SGPT (0-32u/l)	1.yes 2. no		
2. Hypothyroidism Normal range TSH (0.34-4.25 µ IU/ml)	1.yes 2.no		
3. Hyper Uric acid level Normal range U/A Female (2.5-5.6 mg/dl) Male (3.1-7.0 mg/dl)	1.yes 2.no		
4. Hypokalemia Normal range of K(3.5-5.0meq/l)	1.yes 2. no		
5. Hyperkalemia Normal range of K(3.5-5.0meq/l)	1.yes 2.no		
6. Elevated Creatinine(cr) Normal range of Creatinine Female (0.5-0.9 mg/dl) Male (0.6-1.2 mg/dl)	1.yes 2.no		
7. Anemia Normal range of hemoglobin	1.yes 2.no		

Female (12.0-15.8 g/dl) Male (13.3-16.2 g/dl)			
37.	What was the outcome of the patient with regard to the adverse effect?	1. Ancillary medication given 2. Drug dose decreased 3. The suspected Drug holding 4. Totally all drug holding 5. Suspected drug changed 6. Died 7. Defaulted	

Declaration

I, the undersigned, MPH student declare that this research proposal is my original work in partial fulfillment of the requirement for the degree of Master in public health.

Name: Melaku Tadesse

Signature: _____

Place of submission: Institution of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This research proposal work has been submitted for examination with our approval as university advisor(s).

Advisors name	**Signature**
1. Dr. Takele Tadesse (PhD)	_____
2. Mr. Kefyalew Addis (MPH)	_____